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EXAMINER

RAMIREZ, DELIA M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/459,573

Applicant(s)

LIVSHITS ET AL.

Examiner

Delia M. Ramirez

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 45-53 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Status of the Application

Claims 45-53 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/2003 has been entered.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to RUSSIAN FEDERATION 98124016 filed on 12/30/1998, and RUSSIAN FEDERATION 99104431 filed on 03/09/1999.

Claim Objections

2. Claim 45 is objected to because of the following informalities: for clarity, the term "having an ability to produce" should be replaced with "having the ability to produce".
Appropriate correction is required.

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3. Claim 45 is objected to because of the following informalities: for clarity, the term “increasing a copy number of a DNA” should be replaced with “increasing the copy number of a DNA”. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 45-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 45 (claims 46-53 dependent thereon) is indefinite in the recitation of “DNA which hybridizes with the nucleotide sequence shown in SEQ ID NO: 9” for the following reasons. As known in the art, a sequence is a graphical representation of the order in which nucleotides/amino acids are arranged in a molecule. Since hybridization only occurs among molecules, it is unclear as to how a nucleic acid molecule can hybridize to a sequence. It is suggested that the term “nucleotide sequence” be replaced with “polynucleotide”. For examination purposes, the suggested language will be used for claim interpretation. Correction is required.

7. Claim 45 (claims 46-53 dependent thereon) is indefinite in the recitation of “wherein an expression amount of at least one protein selected from the group consisting ofis increased relative to a strain MG1655 or W3110 by increasing a copy number ...” for the following reasons. First, the items being compared are not of the same nature. As written, the expression

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of a protein is compared to a bacterial strain. If the intended comparison is between expression levels of a protein in different bacterial strains, the claim should be amended to clearly indicate what is being compared. Furthermore, even if it is assumed that the intended meaning of the term is “wherein the expression of at least one protein selected from the group consisting ofis increased relative to the expression of said protein in the E. coli strain MG1655 or W3110”, the term is still unclear and confusing since one cannot determine if the comparison refers to the expression of the protein in the wild-type MG1655 or the W3110 strains (i.e. no plasmids or vectors, no additional transformations) or if it includes expression of the protein in any E. coli MG1655 or W3110 (i.e. containing vectors or other modifications not present in the wild-type strain). In addition, as written, it is unclear if the scope of the claim includes the method being practiced with E. coli MG1655 or W3110 transformed with a vector comprising a polynucleotide encoding the polypeptide of SEQ ID NO: 10 or variant thereof as recited in the claim. If the intended meaning of the term is “wherein the expression of at least one protein selected from the group consisting ofis increased by increasing the copy number of a DNA encoding said protein in a cell....”, the claim should be amended accordingly. For examination purposes, the interpretation above will be used. Correction is required.

8. Claim 45 (claims 46-53 dependent thereon) is indefinite in the recitation of “DNA coding for said protein in a cell or by replacing a promoter with a stronger promoter for expression...” for the following reasons. As written, it is unclear if the promoter being replaced is the native promoter (i.e. that of the yahN gene) or any promoter. In addition, the term “in a cell” is unclear since one cannot determine which cell is being used to increase the copy number. For examination purposes, it will be assumed that the promoter being replaced is that of the yahN

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gene and that the term "in a cell" refers to "in the Escherichia bacterium". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 45-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

11. Claims 45-53, as amended, are directed in part to a method of producing L-proline, L-lysine and L-glutamic acid using an Escherichia cell wherein the expression of a polypeptide encoded by a polynucleotide which can hybridize to the polynucleotide of SEQ ID NO: 9 at 60 C, 1xSSC and 1% SDS is increased. The Examiner has been unable to find adequate support for hybridization at 60 C, 1xSSC and 1% SDS. Thus there is no indication that the claimed method using an Escherichia cell wherein the expression of a polypeptide encoded by a polynucleotide which can hybridize to the polynucleotide of SEQ ID NO: 9 at 60 C, 1xSSC and 1% SDS is increased was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

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12. It is noted that the hybridization conditions in canceled claim 1 were: 60 C, 1xSSC and 0.1% SDS.

13. Claims 45-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Claim 45-53 are partially directed to a method to produce L-proline, L-lysine, and L-glutamic acid using an Escherichia cell wherein the expression of a genus of proteins (from any source) encoded by polynucleotides which can hybridize to the polynucleotide of SEQ ID NO: 9 at 60 C, 1xSSC and 1% SDS, is increased by increasing the copy number of said polynucleotides or by using a strong promoter, and wherein said proteins have the activity of excreting L-proline, L-lysine, and L-glutamic acid. While the specification teaches that the polypeptide of SEQ ID NO: 10 (yahN gene product) is homologous to the C. glutamicum lysE transporter protein (page 23, line 25-page 24, line 2), no disclosure has been made of a single proline or glutamic acid excreting protein. In addition, there is no disclosure of the critical structural elements required in a polynucleotide which hybridizes to the polynucleotide of SEQ ID NO: 9 under the conditions recited in the claims to encode a polypeptide having the activity of excreting L-proline or L-glutamic acid. Furthermore, while the specification discloses the production of L-lysine, L-proline and L-glutamic acid with an Escherichia cell wherein the expression of a lysE homolog is increased, no disclosure has been made of a method of

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producing L-lysine, L-proline or L-glutamic acid using an Escherichia cell wherein the expression of a protein able to excrete proline or glutamic acid is increased as recited in the claims.

A adequate written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The recited structural feature of the genus (i.e., hybridizes with the polynucleotide of SEQ ID NO: 9 under stringent conditions of 60 C, 1xSSC and 1%SDS) does not constitute a substantial portion of the genus since the structure of a proline or a glutamic acid excreting protein is completely undefined and the specification does not define the structural features necessary for members of the genus to be selected (i.e. structural elements specific to proline or glutamic acid excreting proteins). The specification discloses only a single species of the claimed genus (i.e., the polynucleotide of SEQ ID NO:9 encoding a lysE functional homolog) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus of polynucleotides required to practice the claimed method. In addition, as indicated above, there is no disclosure of a method to produce L-lysine using an Escherichia cell wherein the expression of a proline or glutamic acid excreting protein is increased. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at the USPTO website.

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14. Claims 45-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing L-proline, L-lysine and L-glutamic acid by cultivating an Escherichia cell which has been modified such that (1) the copy number of a DNA encoding the polypeptide of SEQ ID NO: 10 or a DNA which hybridizes to the polynucleotide of SEQ ID NO: 9 at 60 C, 1xSSC and 0.1%SDS and encodes a protein with lysine transport activity is increased or (2) the expression of said DNA is not under the control of its native promoter but it is under the control of any strong promoter, does not reasonably provide enablement for said method wherein the Escherichia cell has been modified such that (1) the copy number of a DNA which hybridizes to the polynucleotide of SEQ ID NO: 9 and encodes any proline or any glutamic acid excreting protein is increased or (2) the expression of said DNA is not under the control of its native promoter but it is under the control of any strong promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the large number of unknown polynucleotides which encode proline or glutamic acid excreting proteins (from any source) required to practice the claimed invention.

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While the specification discloses the lysE homolog of SEQ ID NO: 10 and its corresponding polynucleotide (SEQ ID NO: 9), it is unclear as to how one can practice the claimed invention in the absence of any information in regard to the structure of a proline or glutamic acid excreting protein. Since structure determines function, one of skill in the art would require some knowledge or guidance as to how structure correlates with the desired function. In the instant case, there is not a single proline or glutamic acid excreting protein disclosed nor there is any teaching as to the structural elements required in a polynucleotide which hybridizes to the polynucleotide of SEQ ID NO: 9 under the conditions recited in the claims to encode a proline or glutamic acid excreting protein. Furthermore, there is no description of a method to produce L-lysine, L-proline or L-glutamic acid as claimed using an Escherichia cell wherein the expression of a proline or glutamic acid excreting protein is increased as recited in the claims. While the argument can be made that one could expect (1) an increase in the production of L-proline if the expression of an L-proline excreting protein is increased, and (2) an increase in the production of L-glutamic acid if the expression of a glutamic acid excreting protein is increased, it is unclear as to how one can reasonably expect (1) an increase in L-lysine production by increasing the expression of a proline or glutamic acid excreting protein, (2) an increase in L-proline production by increasing the expression of a glutamic acid excreting protein, or (3) an increase in L-glutamic acid production by increasing the expression of a proline excreting protein. Even the specification discloses that the overexpression of the yahN gene (SEQ ID NO: 9; lysE homolog) did not result in enhanced production of all amino acids but rather L-lysine, L-proline and L-glutamic acid, therefore indicating the unpredictability of the art in regard to enhancing the production of one amino acid with the overexpression of another amino

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acid excreting protein. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to have a proline or glutamic acid excreting function, and the unpredictability of the art in regard to enhancing the production of one amino acid by overexpressing another amino acid excreting protein, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) isolate polynucleotides which encode any proline or glutamic acid excreting proteins, and (2) determine if an increase in the expression of said excreting proteins result in enhanced production of L-lysine, L-proline or L-glutamic acid. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 45-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blattner et al. (GenBank accession number P75693, November 1, 1997) in view of Vrljic et al. (Mol. Microbiol. 22:815-826, 1996) and Kojima et al. (U.S. Patent No. 6040160, 102(e) date 5/29/1996).

Blattner et al. teaches an *E. coli* polypeptide which is 100% identical to that of SEQ ID NO: 10. Blattner et al. teaches that the polypeptide is a transmembrane protein and that it belongs to the *lysE* protein family based on structural homology. The polynucleotide encoding the polypeptide of Blattner et al. would hybridize to the polynucleotide of SEQ ID NO: 9. Blattner et al. does not teach increased expression of the polypeptide to enhance amino acid production.

Vrljic et al. teaches the isolation of the *C. glutamicum lysE* gene (page 817) and the characterization of the gene product, *lysE*, as a lysine transporter protein (page 818, second column, page 820, first column). Vrljic et al. also teaches that overexpression of the *lysE* gene results in enhanced lysine export to the growth medium (page 819, Figure 5). Vrljic et al. does not teach the *E. coli* polypeptide of SEQ ID NO: 10 or the production of L-lysine, L-proline, or L-glutamic acid by overexpression of the *E. coli lysE* homolog.

Kojima et al. teaches a method of producing L-lysine by using an *Escherichia* cell transformed with a vector encoding a mutated aspartokinase III (Abstract). Kojima et al. also teaches that the DNA encoding the mutant aspartokinase III can be introduced in a host cell by using a multicopy vector (column 12, lines 50-59) or it can be inserted in the chromosome of a

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host organism by using a transposon (column 12, line 66-column 13 line 5) and that the mutated aspartokinase III can be expressed using inducible promoters such as lac, trp, and PL (column 12, lines 60-65). In addition, Kojima et al. teaches that (1) *Corynebacteria* and *E. coli* are used for industrial production of L-lysine (column 1, lines 11-23), (2) expressing a *C. glutamicum* polypeptide in *E. coli* requires reducing growth temperature (column 1, lines 40-55) and (3) expression of a gene from a heterologous organism in *E. coli* may be problematic due to the possible decomposition of the expression product by proteases as well as the formation of inclusion bodies (column 1, line 59-column 2, line 4). Kojima et al. does not teach a method for producing L-lysine with the *E. coli* lysE homolog.

Claims 45, 49-50 and 51 are partially directed to a method for producing L-lysine by using an *Escherichia* cell wherein the expression of the polypeptide of SEQ ID NO: 10 or the expression of an L-amino acid excreting protein encoded by a DNA which hybridizes to the polynucleotide of SEQ ID NO: 9 under the conditions recited in the claim is increased by increasing the copy number of its coding polynucleotide, or by replacing the native promoter of said polynucleotide with any stronger promoter. Claims 46-48 add the limitation that the copy of the coding polynucleotide be increased by using a multicopy vector or a transposon.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the polynucleotide of Blattner et al. in a multicopy vector or a transposon, as taught by Kojima et al., transform an *Escherichia* cell as taught by Kojima et al., and cultivate said cell to produce L-lysine as taught by Vrljic et al. A person of ordinary skill in the art is motivated to construct such a vector or transposon, and transform an *E. coli* cell in order to increase the transport of L-lysine in the growth medium in view of the teachings of Vrljic et al.

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and Kojima et al. and produce large amounts of L-lysine. One of ordinary skill in the art has a reasonable expectation of success at constructing the vector or transposon, transforming an E. coli cell and producing L-lysine since Vrljic et al. teaches the production of L-lysine by overexpressing the *C. glutamicum* lysE gene (lysine transport protein) and Kojima et al. teaches that it is preferable to use E. coli if the gene to be overexpressed is isolated from E. coli. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

18. This rejection was previously applied to now canceled claims 1-2, 11-13 and 27 and is now applied to newly added claims 45-51 for the reasons set forth above.

19. Applicants argue that the combination of references above fails to teach or suggest the claimed method. Specifically, Applicants argue that Blattner et al. does not demonstrate that the YAHN polypeptide (SEQ ID NO: 10) is actually an L-amino acid excreting protein and that it is not reasonable to expect from the cited reference that the YAHN polypeptide participates in amino acid excretion. It is Applicant's contention that in view of the unexpected results in regard to improved L-amino acid production, this rejection should be withdrawn.

20. Applicant's arguments have been fully considered as they relate to newly added claims 45- 51 but are not deemed persuasive to avoid the rejection. While it is agreed that Blattner et al. do not experimentally demonstrate that the YAHN protein is an L-amino acid excreting protein, Blattner et al. suggests that such protein is a lysE homolog. Furthermore, the YAHN polypeptide of Blattner et al. is 100% sequence identical to that of the instant claims therefore it would inherently exhibit amino acid export function. While the Examiner agrees that the results obtained in regard to the production of L-proline and L-glutamic acid are unexpected, the

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Examiner disagrees with Applicant's contention that the results disclosed in the specification in regard to the production of L-lysine are unexpected in view of the fact that Vrljic et al. teaches the production of L-lysine by overexpressing a lysine excreting protein (lysE) and Blattner's suggestion that the polypeptide of SEQ ID NO: 10 is a lysE homolog. Therefore, as indicated above, the claimed invention is deemed obvious over the combined teachings of the references cited.

Conclusion


21. No claim is in condition for allowance.
22. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.
23. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR/July 21, 2003


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